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EXAMINER	
BLAND, LAYLA D	
ART UNIT	PAPER NUMBER
1623	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/552,309	LEBRETON, PIERRE	
	Examiner	Art Unit	
	LAYLA BLAND	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 February 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17,20-24,26-28,30,31 and 33-42* is/are pending in the application.

4a) Of the above claim(s) *28,30,31,41 and 42* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17,20-24,26,27 and 33-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date ____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This office action is a response to Applicant's amendment submitted February 2, 2009, wherein claims 17, 20-24, 26-28, and 30 are amended, claims 18-19, 25, 29, and 32 are canceled, and claims 33-42 are newly submitted. Claims 17, 20-24, 26-28, 30-31, and 33-42 are pending.

Claims 28, 30, and 31, and new claims 41 and 42 which depend from claim 28, are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on June 4, 2008. It is noted that claims 28, 30, and 31 do not have the proper status identifier of "withdrawn."

Claims 17, 20-24, 26-27, and 33-40 are examined on the merits herein.

In view of the cancellation of claims 18-19, 25, 29, and 32, all rejections made with respect to those claims in the previous office action are withdrawn.

In view of Applicant's amendment submitted February 2, 2009, the rejection of claims 17-27 under 35 USC 112, second paragraph, for being indefinite is withdrawn. The indefinite limitations are no longer in the claims or have been clarified by amendment.

The rejection of claims 17, 26, and 27 are rejected under 35 U.S.C. 102(b) as being anticipated by Kuniak is withdrawn because the amended claims require cross-linking of HA.

The following new rejection was necessitated by Applicant's amendment submitted February 2, 2009, wherein the scope of independent claim 17 was changed to require cross-linking of a mixture of a first hyaluronic acid salt having a first molecular weight and a second hyaluronic acid salt having a second molecular weight.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 17, 20-24, 26-27, and 33-40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 17 and dependent claims 20-24, 26-27, and 33-40 are drawn to a process which comprises cross-linking a mixture of a first HA salt having a first molecular weight and a second HA salt having a second molecular weight. These limitations are unclear because HA has molecular weight dispersity. Thus, the first HA salt, having the first molecular weight, contains not only molecules of the recited molecular weight, but many other molecules of lower and higher molecular weights. Depending on the polydispersity of the HA product, those molecules of lower and higher molecular weights may be much lower or much higher, and may make up a small or large portion of the total amount. Thus, if the "first" HA has a molecular weight of 3×10^5 as recited in claim 34, depending on the polydispersity of the product, the product will contain a small or large number of molecules which have a significantly higher molecular weight.

Likewise, if the "second" HA has a molecular weight of 3×10^6 as recited in claim 34, that product will contain a small or large number of molecules which have a significantly smaller molecular weight. Thus, there will be overlap between the higher molecular weight molecules present in the “first” HA product and the lower molecular weight molecules present in the “second” HA product, and it is not possible to determine which are of the “first” HA product and which are of the “second” HA product.

In the response dated February 2, 2009, Applicant argues that the claims require two different HA salts, and that the claims refer to two preexisting products. Claims are given their broadest reasonable interpretation. The claims do not contain a limitation for how the mixture is formed and do not require preexisting products. Claim 17 only requires a *mixture* of a "first" HA and a "second" HA, and that mixture cannot be differentiated into a "first" and "second" HA, as set forth above. The examples in the specification describe how two separate HA products are weighed out in particular proportions and then cross-linked. The Examiner recommends that the claims be amended to include a method step for formation of the mixture from two separate products, which would clarify the contents of the “mixture” of the “first" and “second” HA.

The following rejections are maintained and modified for relevancy to the amended claim set:

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 17, 20, 23, 24, 26, 27, 33, 37, 38, and 39 are rejected under 35 U.S.C. 102(b) as being anticipated by Balazs (US 4,582,865, PTO-1449 submitted October 7, 2005), or Balazs (US 4,582,865, PTO-1449 submitted October 7, 2005).

Balazs teaches the cross-linking of sodium hyaluronates having varying molecular weights using divinyl sulfone in aqueous sodium hydroxide [columns 5 and 6, Examples1-5]. The ratio of HA/DVS was about 4.7 by weight [Example 1], or 0.2-2.0 by mole [Example 4]. A mixture comprising a first HA having a first molecular weight and a second HA having a molecular weight higher then of the first HA is indefinite, as set forth above. However, the skilled artisan knows that hyaluronans have molecular weight dispersity, and thus it can be considered that a lower molecular weight HA was crosslinked with a higher molecular weight HA. Claim 23 requires that more than 50% by weight is of the first HA and less than 50% by weight is of the second HA. Claim 17 only requires that the molecular weight of the second HA is higher than the molecular weight of the first HA. Thus, because HA has molecular weight dispersity, it is inherent that half the HA will have a higher molecular weight than the other half. Likewise, the HA will inherently comprise at least 5% (as recited in claim 24) by weight of molecules which have a higher molecular weight than other molecules; and will inherently

comprise 30% of molecules which have a higher molecular weight than the other 70% (as recited in claim 37).

It is noted that claim 39 does not require that the cross-linking reagent is an aldehyde, but only to limit the aldehydes which are recited in alternative to the other reagents recited in claim 38. Thus, claim 39 is also anticipated.

Response to Arguments

Applicant argues that the instant claims are drawn to the use of two preexisting HA products, which is different from one product which may have molecular dispersity. This argument is not persuasive because the claims are simply drawn to a mixture of a first HA and a second HA, wherein the molecular weight of the second HA is greater than that of the first HA. A molecular disperse HA product meets that limitation. The claims do not include a limitation for preparation of the mixture from two different preexisting products, as was done in the examples in the instant specification.

Claims 17, 20, 23, 24, 26, 27, 33, and 37-40 are rejected under 35 U.S.C. 102(b) as being anticipated by Mälson (US 4,716,154, December 29, 1987, PTO-1449 submitted October 7, 2005).

Mälson teaches a gel of crosslinked hyaluronic acid [see abstract]. Sodium hyaluronate (400 mg) of molecular weight about 1×10^6 was dissolved in aqueous sodium hydroxide and cross-linked using 300 µL of 1,4-butanediol diglycidyl ether (BDDE) (same as 1,4-bis(2,3-epoxypropoxy)butane) [column 5, Example 3]. Similar procedures were carried out using HA of molecular weight 3×10^6 [column 4, Example

1], 20,000 [column 5, Example 3], and 3 x 10^6 [column 5, Example 5]. A mixture comprising a first HA having a first molecular weight and a second HA having a molecular weight higher then of the first HA is indefinite, as set forth above. However, the skilled artisan knows that hyaluronans have molecular weight dispersity, and thus it can be considered that a lower molecular weight HA was crosslinked with a higher molecular weight HA. Claim 23 requires that more than 50% by weight is of the first HA and less than 50% by weight is of the second HA. Claim 17 only requires that the molecular weight of the second HA is higher than the molecular weight of the first HA. Thus, because HA has molecular weight dispersity, it is inherent that half the HA will have a higher molecular weight than the other half. Likewise, the HA will inherently comprise at least 5% (as recited in claim 24) by weight of molecules which have a higher molecular weight than other molecules; and will inherently comprise 30% of molecules which have a higher molecular weight than the other 70% (as recited in claim 37). The amounts of BDDE required to achieve gel formation are also taught [column 5, Table].

It is noted that claim 39 does not require that the cross-linking reagent is an aldehyde, but only to limit the aldehydes which are recited in alternative to the other reagents recited in claim 38. Thus, claim 39 is also anticipated.

Response to Arguments

Applicant argues that the instant claims are drawn to the use of two preexisting HA products, which is different from one product which may have molecular dispersity. This argument is not persuasive because the claims are simply drawn to a mixture of a

first HA and a second HA, wherein the molecular weight of the second HA is greater than that of the first HA. A molecular disperse HA product meets that limitation. The claims do not include a limitation for preparation of the mixture from two different preexisting products, as was done in the examples in the instant specification.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 21, 22, 35, and 36 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Mälson (US 4,716,154, December 29, 1987, PTO-1449 submitted October 7, 2005).

Mälson teaches as set forth above.

Mälson does not expressly teach the crosslinking of a hyaluronic acid salt of molecular weight of at most 9.9×10^5 and a hyaluronic acid salt of molecular weight of at least 10^6 Da. However, the skilled artisan knows that hyaluronans have molecular weight dispersity, and that HA having a molecular weight about 1,000,000 is extremely likely to contain HA molecules of molecular weight less than 990,000, including 10^4 - 9.9×10^5, and HA molecules of molecular weight more than 1,000,000, including 10^6-10^8 and including 1.1×10^6 - 5×10^6. The recitation of intrinsic viscosity in claim 22 is an intrinsic property of the composition and cannot be separated from it.

Response to Arguments

Applicant argues that the instant claims are drawn to the use of two preexisting HA products, which is different from one product which may have molecular dispersity. This argument is not persuasive because the claims are simply drawn to a mixture of a first HA and a second HA, wherein the molecular weight of the second HA is greater than that of the first HA. A molecular disperse HA product meets that limitation. The claims do not include a limitation for preparation of the mixture from two different preexisting products, as was done in the examples in the instant specification.

Claim 34 is rejected under 35 U.S.C. 103(a) as being unpatentable over Mälson (US 4,716,154, December 29, 1987, PTO-1449 submitted October 7, 2005).

Mälson teaches as set forth above. Mälson also teaches that HA has molecular weight varying within the range of 20,000 to 8,000,000 and that it is an easy matter to properly adapt the concentration, type of crosslinking agents employed and degree of crosslinking to the molecular weight of each particular starting material. If HA has a low molecular weight, greater concentration of HA and cross-linking agent will be needed as compared to HA which has a high molecular weight. A preferred range is from 500,000 to 3,000,000 [column 2, line 62 - column 3, line 17].

Mälson does not explicitly teach cross-linking of a mixture composed of 90% of a first HA of a particular molecular weight and about 10% of a second HA having a higher particular molecular weight. A mixture comprising a first HA having a first molecular weight and a second HA having a molecular weight higher then of the first HA is

indefinite, as set forth above, and it is not possible to ascertain whether Mälson's procedure results in such a mixture. However, it would have been obvious to one of ordinary skill in the art at the time the invention was made to optimize the conditions taught by Mälson to arrive at a mixture comprising different molecular weights of HA. Mälson teaches the effect of molecular weight on reaction conditions, as set forth above. Mälson also provides guidance regarding the solids content of gel formation from HA of differing molecular weights [columns 4-6, Examples 1-10]. Thus, the skilled artisan could easily manipulate these in order to prepare a crosslinked HA gel having desired characteristics.

Further, the Supreme Court has determined, in *KSR International Co. v. Teleflex, Inc.*, 550 U.S._, 82, USPQ2d 1385 (2007), that "a person of ordinary skill attempting to solve a problem will" not" be led only to those elements of prior art designed to solve the same problem ..... " (KSR, 550 U.S. at_, 82 USPQ2d at 1397). In addition, the court found that "When a work is available in one field of endeavor, design incentives and other market forces can prompt variations of it, either in the same field or a different one. If a person of ordinary skill can implement a predictable variant, 35 USC 103 likely bars its patentability" (KSR, 550 U.S. at_, 82 USPQ2d at 1396). Further the court found that the Federal Circuit has erred in applying the teaching-suggestion-motivation test in an overly rigid and formalistic way, in particular by concluding "that a patent claim cannot be proved obvious merely by showing that the combination of elements was 'obvious to try'" (KSR, 550 U.S. at_, 82 USPQ2d at 1397) and has further determined that "..... [t]he combination of familiar elements according to known methods is likely to

be obvious when it does no more than yield predictable results" (KSR, 550 U.S. at_, 82 USPQ2d at 1395). The court further found that ". ..... the conclusion that when a patent simply arranges old elements with each performing the same function it had been known to perform and yields no more than one would expect from such an arrangement, the combination is obvious" (KSR, 550 U.S. at_, 82 USPQ2d at 1395-1396). Thus, when considering obviousness of a combination of known elements, the operative question is "whether the improvement is more than the predictable use of prior art elements according to their established functions" (KSR, 550 U.S. at_, 82 USPQ2d at 1396). In the instant case, the claimed invention is seen as the predictable use of prior art elements (crosslinking HA of different molecular weights) according to their established functions (gel formation). The claimed invention could also be seen as arranging old elements (crosslinking HA of different molecular weights) with each performing the same function it had been known to perform (gel formation), and thus is obvious.

Response to Arguments

Applicant argues that Mälson discloses cross-linking of only one HA product, and that the Examiner did not set forth a reason to modify Mälson's process. As set forth above, the claimed process is not clear and does not contain limitations for the preparation of the mixture. Thus, Mälson's "one product" could be considered a mixture of several different products because HA contains molecules of varying molecular weights. As set forth above, Mälson teaches that HA products of widely varying molecules weights may be used for the same purpose, and provides guidance for how

to optimize the process for HA of different molecular weights. The reason to use HA of different molecular weights is because Mälson teaches it can be done, how to do it, and the utility of the resulting composition.

Applicant argues that the results of the claimed invention were not predictable, and that cross-linking two different types of polymers provides improved properties for an injectable hydrogel product. This argument is not persuasive because "objective evidence of nonobviousness must be commensurate in scope with the claims which the evidence is offered to support." See MPEP 716.02(d). In this case, the polymers having improved properties, as in Examples 3 and 4 of the instant specification, were prepared by a specific process which is not commensurate in scope with the claims. The claims are drawn to a "mixture" of a "first" and "second" HA, but do not recite limitations for how to prepare that mixture. As set forth above, the identity of that mixture is not clear. Furthermore, Examples 3 and 4 are drawn to the use of preexisting HA of particular molecular weights, which are not recited in the broad claims. The broad claims only require that one is higher than the other, but do not require how much difference in molecular weight must be present. Thus, even if the claims clearly required the use of two preexisting HA products (which they do not, at this time), cross-linking of two separate HA products wherein one molecular weight is 1×10^6 and the other is 1.1×10^6, for example, would not likely result in products having the improved properties because the disparity in molecular weight is so small. In addition, it appears that the ratio of high/low HA in Examples 3 and 4 impacts the properties of the hydrogel. The product of Example 3, prepared from the approximately 70/30 mixture, has a

remanence index of 3.6 while the product of Example 4, prepared from the 90/10 mixture, has a remanence index of 7.7. Thus, it is unclear which ratios would result in products having the desired characteristics and which would not. For these reasons, the rejection is maintained.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to LAYLA BLAND whose telephone number is (571)272-9572. The examiner can normally be reached on Monday - Friday, 7:00 - 3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on (571) 272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Shaojia Anna Jiang/
Supervisory Patent Examiner, Art Unit 1623

/Layla Bland/
Examiner, Art Unit 1623